

Effect of Allopurinol in Decreasing Proteinuria in Type 2 Diabetic Patients

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Introduction. Diabetic nephropathy is the most prevalent cause of end-stage renal disease. Besides factors such as angiotensin II, cytokines, and vascular endothelial growth factor, uric acid may play a role as the underlying cause of diabetic nephropathy. We evaluated allopurinol effects on proteinuria in diabetic patients with nephropathy.

Materials and Methods. In a double-blinded randomized controlled trial on 40 patients with type 2 diabetes mellitus and diabetic nephropathy (proteinuria, at least 500 mg/24 h and a serum creatinine level less than 3 mg/dL), allopurinol (100 mg/d) was compared with placebo. Administration of antihypertensive and renoprotective drugs (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers continued for both groups, without changes in dosage. Proteinuria was compared at baseline and 2 and 4 months between the two groups.

Results. Each group consisted of 9 men and 11 women. There were no difference between two groups regarding age, body mass index, duration of diabetes mellitus, systolic and diastolic blood pressure, fasting blood glucose, blood urea nitrogen, serum creatinine, serum potassium, and urine volume. Serum levels of uric acid ($P = .02$) and 24-hour urine protein ($P = .049$) were significantly lower in the patients on allopurinol, after 4 months of receiving allopurinol, compared with the control group.

Conclusions. Low-dose allopurinol can reduce severity of proteinuria after 4 months of drug administration, which is probably due to decreasing the serum level of uric acid. Thus, allopurinol can be administered as an adjuvant cost-effective therapy for patients with diabetic nephropathy.

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INTRODUCTION

Incidence of diabetic nephropathy is the same for type 1 and 2 diabetes mellitus (DM), and approximately 20% to 30% of diabetic patients are affected by nephropathy, 15 years after the beginning of DM.¹ Hypertension and glomerular hyperfiltration contribute to the development of diabetic nephropathy.^{2,3} Activation of cytokines,

profibrotic factors, inflammation, and vascular endothelial growth factor (VEGF) may also play some roles in occurrence and progression of diabetic nephropathy.^{4,5} Genetic susceptibility, age, poor glycemic control, some ethnic groups, obesity, and smoking are some other factors associated with diabetic nephropathy.⁶⁻⁹

A study carried out in Taiwan on patients with

type 2 DM demonstrated that serum level of uric acid in these patients directly correlated with the level of urinary albumin excretion, and the serum uric acid level of patients was higher compared with healthy people.¹⁰ Hyperuricemia may cause periglomerular vascular injury, glomerular hypertension, and reduced kidney perfusion, which consequently can lead to interstitial fibrosis.¹¹⁻¹³ In patients with type 2 DM, hyperuricemia may be accompanied by peripheral vascular disease, hypertension, hypertriglyceridemia, higher level of hemoglobin A1c, more severe albuminuria, lower glomerular filtration rate (GFR), and early start or rapid progression of diabetic nephropathy. Prevalence of hyperuricemia is especially high in diabetic women.¹⁴⁻¹⁶

A study on hypertensive rats demonstrated that allopurinol decreased renal injury, which could be due to inhibition of lipid peroxidation.¹⁷ In hyperuricemic rats, elevation of serum renin and increased activity of cyclooxygenase 2 in periglomerular arterioles were noted. Allopurinol, by decreasing the level of serum uric acid, reduced the histological changes and improved kidney function.¹³

Concerning the higher level of serum uric acid in diabetic patients and also its role in causing vascular and glomerular injuries, decreasing GFR, we evaluated the role of allopurinol in patients with type 2 DM and nephropathy. The aim of our study was to evaluate the effect of allopurinol in decreasing of proteinuria in type 2 diabetic patients with nephropathy.

MATERIALS AND METHODS

Patients

This was a double-blinded randomized controlled trial on 40 patients with type 2 DM and nephropathy (at least 500 mg/24 h) at the nephrology clinics of Isfahan, from August 2006 to May 2008. The study was approved by Isfahan University's ethic committee. Patients were enrolled by simple random allocation to the study or control group, so that 20 patients were included in each group. Sample size was determined 20 patients in each group, using a 5% significance level, a power of 80% and 800 mg reduction in 24-hour urine protein of the control group.

To evaluate diabetic nephropathy, ophthalmologic evaluation was done for all patients. The inclusion

criteria were an age over 18 years old, proteinuria greater than 500 mg/24 h, bilateral normal-size kidney on ultrasonography (9 cm to 12 cm), existence of diabetic retinopathy, and absence of systemic diseases or other causes of proteinuria based on physical examination and history. The exclusion criteria were as follows: administration of allopurinol for another reason, significant renal insufficiency (serum creatinine > 3 mg/dL or GFR < 25 mL/min), development of allopurinol side effects (elevated liver enzymes, cytopenia, and dermatitis), and uncooperativeness during the study. In nephrology clinics, 520 records of type 2 diabetic patients were reviewed and 50 patients that met the inclusion criteria were selected, of whom 44 patients agreed to enter the study. During the study, 4 patients (2 in each group) were excluded due to in compliance.

Methods

The patients received allopurinol tablet (100 mg) or placebo, once per day, for 4 months. Both allopurinol and placebo were produced by the Mehr-daru Pharmaceutical Company, Iran. All of the patients who received antihypertensive drugs, angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs) continued them with the same schedule and dosage. If administration of new antihypertensive drugs were indicated, drugs without effects on proteinuria, such as beta blockers, were prescribed. All of the participants were using renoprotective drugs such as ACEIs and/or ARBs. Hyperglycemia treatment consisted of oral hypoglycemic agents (OHA) and/or insulin, which continued during the study with the same dose.

At baseline and also 2 and 4 months later, the participants were visited for evaluation of vital signs and results of laboratory tests. The following tests were performed for the patients: complete blood count, fasting blood glucose, blood urea nitrogen (BUN), serum creatinine, serum potassium, serum uric acid, serum aspartate aminotransferase and alanine aminotransferase, urinalysis, and 24-hour urine volume, protein, and creatinine. The blood count test was performed by H1 or SYSMEX (Tokyo, Japan), while fasting blood glucose, liver and kidney function parameters, and uric acid level were measured by an RA 1000 analyzer (Technicon Instrument, New York, NY, USA)

using Pars Azmoon kits (Tehran, Iran), and serum potassium, by Flame photometer (Eppendorf, Germany). The 24-hour urine protein was measured by trichloroacetic acid method, using a photometer (model ECOM-E G125, Eppendorf, Germany).

Statistical Analyses

The collected data were analyzed by descriptive indexes (mean \pm standard deviation), the *t* test, the nonparametric Friedman test, and the Spearman correlation coefficient, using the SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Ill, USA). To analyze the data, normal distribution test was performed; if the distribution was normal, then repeated measured analysis of variance was used. Otherwise, nonparametric tests including the Friedman and Mann-Whitney tests were used.

RESULTS

Table 1 demonstrates the demographic information of the patients. Each group consisted of 9 men and 11 women. The age of the patients was from 30 to 77 years with the mean of 57.7 ± 10.5

years. The weight of the patients ranged from 62 kg to 110 kg in study group and 43 kg to 100 kg in the control group. The mean weight was significantly higher in the study group than in the control group ($P = .045$). Duration of DM was between 2 and 29 years (mean, 12.6 ± 6.7 years).

Based on repeated measure analysis of variance, patients in the study and control groups were not significantly different in terms of systolic and diastolic blood pressure, fasting blood glucose, blood urea nitrogen, serum creatinine, serum potassium, urine glucose, and urine volume levels during the study period (Table 2). The 24-hour urine creatinine level was significantly higher in the study group at baseline ($P = .02$), but there was no significant difference between the two groups at 2 and 4 months of the study.

Regression analysis showed that the higher level of urine creatinine concentration in the study group was due to the higher weight of this group. Generally, the mean urine creatinine in the study group was higher than that of the control group in all stages, but the difference was significant only at baseline. The two groups were not significantly different regarding serum levels of uric acid ($P = .35$), but at 4 months, serum uric acid levels of the study group were significantly lower than those of the control group ($P = .02$; Figure 1). At baseline and 2 months of the study, 24-hour urine protein concentration was not significantly different between the two groups, but at 4 months, urine protein of the study group was significantly lower than that of the control group ($P = .049$; Figure 2).

Finally, no adverse effects were reported by our patients in the allopurinol group during the study.

Table 1. Demographic Characteristics of Patients on Allopurinol and Placebo

Variable	Study Group	Control group
Number of patients	20	20
Gender		
Male	9	9
Female	11	11
Age, y	56.3 ± 10.6	59.1 ± 10.6
Weight, kg	79.7 ± 12.7	71.1 ± 13.6
Body mass index, kg/m ²	28.9 ± 5.1	26.8 ± 4.6
Diabetes mellitus duration, y	11.8 ± 5.7	13.3 ± 7.6

Table 2. Clinical and Biochemical Parameters of Patients on Allopurinol and Placebo During the Study Period

Variable	Baseline			At 2 Months			At 4 Months		
	Study Group	Control Group	P	Study Group	Control Group	P	Study Group	Control Group	P
Systolic blood pressure, mm Hg	145.8 ± 11.3	147.3 ± 16.7	.74	143.8 ± 14.3	149.3 ± 14.7	.24	138.3 ± 9.5	142 ± 13.5	.32
Diastolic blood pressure, mm Hg	88.5 ± 8.6	86.0 ± 8.4	.36	87.8 ± 7.9	87.5 ± 9.1	.93	85.5 ± 7.9	85.3 ± 8.3	.92
Fasting blood glucose, mg/dL	178.4 ± 79.9	151.4 ± 61.7	.23	172 ± 68.9	146.4 ± 52.1	.19	158.3 ± 50.7	149.6 ± 46.3	.58
Blood urea nitrogen, mg/dL	25.9 ± 15.4	30.4 ± 16.0	.04	28.0 ± 15.1	32.5 ± 17.3	.38	38.5 ± 12.7	35.3 ± 24.6	.28
Serum creatinine, mg/dL	1.3 ± 0.45	1.5 ± 0.6	.31	1.3 ± 0.5	1.5 ± 0.6	.17	1.3 ± 0.5	1.6 ± 0.6	.18
Serum potassium, mg/dL	4.85 ± 0.41	4.67 ± 0.44	.18	4.79 ± 0.50	4.63 ± 0.46	.30	4.67 ± 0.35	4.71 ± 0.42	.75
Serum uric acid, mg/dL	5.96 ± 1.21	6.50 ± 2.20	.35	5.49 ± 0.50	6.37 ± 1.85	.06	5.31 ± 0.79	6.44 ± 1.97	.02
24-hour urine protein, mg	1756 ± 1047	1673 ± 997	.80	1268 ± 870	1688 ± 1152	.20	1011 ± 767	1609 ± 1071	.049
24-hour urine creatinine, mg	1203 ± 396	926 ± 322	.02	1154 ± 498	922 ± 338	.09	1091 ± 262	959 ± 355	.19
24-hour urine volume, mL	2383 ± 539	2152 ± 690	.25	2326 ± 538	2132 ± 592	.29	2234 ± 446	2306 ± 625	.68

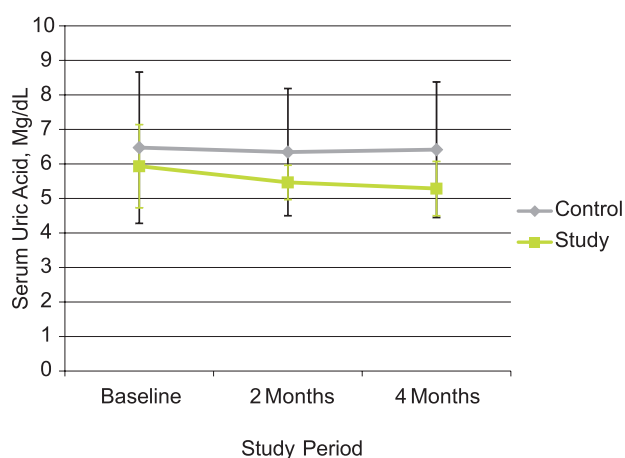


Figure 1. Mean serum levels of uric acid during the study in patients receiving allopurinol (study group) and placebo (control group).

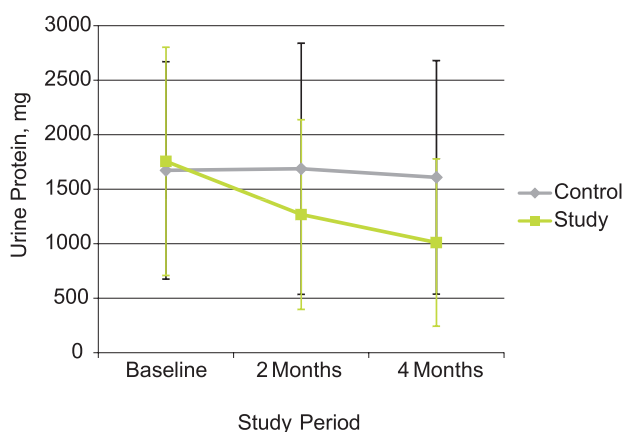


Figure 2. Mean 24-hour urine levels of protein during the study in patients receiving allopurinol (study group) and placebo (control group).

DISCUSSION

Various agents have been used for treatment of diabetic nephropathy including ACEIs, ARBs, lipid-lowering agents, and protein intake restriction. Most studies have proved that ACEIs and ARBs are useful in the treatment of diabetic nephropathy.¹⁸⁻²⁰ Administration of these drugs in microalbuminuria stages resolve albuminuria, but when microalbuminuria develops, these drugs only slow down the progression of diabetic nephropathy and reduce the severity of proteinuria.²¹⁻²³ Concerning the side effects of these drugs, including cough and hyperkalemia, it is not possible to administer these drugs to all patients or at full doses.

According to results of some studies, serum

uric acid level of diabetic patients was higher than that of healthy people.^{10,12} Moreover, some studies indicated that hyperuricemia in diabetic patients was accompanied by vascular complications, albuminuria, and decreased GFR. Thus, decrease in serum uric acid level can probably be effective in treatment of diabetic nephropathy. To the best of our knowledge, there is no report on the therapeutic effect of allopurinol in diabetic nephropathy. Consequently, results of the current study cannot be compared with findings of other similar studies.

In the beginning of the study, the mean serum uric acid level was 5.9 ± 1.2 mg/dL and 6.5 ± 2.2 mg/dL in study and control groups, respectively. The mean serum uric acid level in another study carried out on Taiwanese patients with type 2 DM was 5.2 ± 1.6 mg/dL for patients with normalalbuminuria, 5.6 ± 1.9 mg/dL for patients with microalbuminuria, and 6.7 ± 2.1 mg/dL for patients with macroalbuminuria.¹⁰ The mean serum level of uric acid in our patients was comparable with that of Taiwanese patients with macroalbuminuria.

Administration of allopurinol (100 mg/d) in our study group for 4 months resulted in significant decrease in serum uric acid level and also a significant decrease in proteinuria. It can be concluded that allopurinol, by lowering the serum uric acid, inhibited the effect of uric acid on glomeruli and kidney vasculatures, and consequently, reduced proteinuria. However, in short-term (after 2 months of administration of allopurinol), serum level of uric acid and severity of proteinuria in the study group did not significantly decrease, compared with the control group. Furthermore, allopurinol may have renoprotective effects via the mechanism of reducing the kidney microvasculature endothelial dysfunction. Thus, it can be concluded that low-dose allopurinol (100 mg/d) can reduce severity of proteinuria, and possibly the progression of nephropathy, if administered for longer than 2 months. Administering the drug at this dosage in the study did not bring about any adverse effects, and it seems that long-term treatment of patients with allopurinol is safe.

As all of the patients of the current study were receiving ACEIs or ARBs before and during, we can assume that the additional renoprotective effect (lowering the proteinuria severity) was not related to those drugs. Administration of allopurinol

accompanied with those drugs can synergically increase the renoprotective effect.

CONCLUSIONS

In patients with diabetic nephropathy, allopurinol can be administered for treatment of diabetic nephropathy with no significant side effects. Considering the small sample size of this study, it is recommended that allopurinol effect on proteinuria be investigated further through studies at large scale with various doses of allopurinol and longer course of treatment in diabetic patients with nephropathy.

CONFLICT OF INTEREST

None declared.

REFERENCES

- Orchard TJ, Dorman JS, Maser RE, et al. Prevalence of complications in IDDM by sex and duration. Pittsburgh Epidemiology of Diabetes Complications Study II. *Diabetes*. 1990;39:1116-24.
- Pavkov ME, Knowler WC, Bennett PH, Looker HC, Krakoff J, Nelson RG. Increasing incidence of proteinuria and declining incidence of end-stage renal disease in diabetic Pima Indians. *Kidney Int*. 2006;70:1840-6.
- Hilgers KF, Veelken R. Type 2 diabetic nephropathy: never too early to treat? *J Am Soc Nephrol*. 2005;16:574-5.
- Wolf G, Ziyadeh FN. Molecular mechanisms of diabetic renal hypertrophy. *Kidney Int*. 1999;56:393-405.
- Burns WC, Twigg SM, Forbes JM, et al. Connective tissue growth factor plays an important role in advanced glycation end product-induced tubular epithelial-to-mesenchymal transition: implications for diabetic renal disease. *J Am Soc Nephrol*. 2006;17:2484-94.
- Adler S. Diabetic nephropathy: Linking histology, cell biology, and genetics. *Kidney Int*. 2004;66:2095-106.
- Tapp RJ, Shaw JE, Zimmet PZ, et al. Albuminuria is evident in the early stages of diabetes onset: results from the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). *Am J Kidney Dis*. 2004;44:792-8.
- Nelson RG, Knowler WC, Pettitt DJ, Saad MF, Bennett PH. Diabetic kidney disease in Pima Indians. *Diabetes Care*. 1993;16:335-41.
- Gelber RP, Kurth T, Kausz AT, et al. Association between body mass index and CKD in apparently healthy men. *Am J Kidney Dis*. 2005;46:871-80.
- Tseng CH. Correlation of uric acid and urinary albumin excretion rate in patients with type 2 diabetes mellitus in Taiwan. *Kidney Int*. 2005;68:796-801.
- Sanchez-Lozada LG, Tapia E, Santamaria J, et al. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. *Kidney Int*. 2005;67:237-47.
- Nagahama K, Inoue T, Iseki K, et al. Hyperuricemia as a predictor of hypertension in a screened cohort in Okinawa, Japan. *Hypertens Res*. 2004;27:835-41.
- Kang DH, Nakagawa T, Feng L, et al. A role for uric acid in the progression of renal disease. *J Am Soc Nephrol*. 2002;13:2888-97.
- Tseng CH. Independent association of uric acid levels with peripheral arterial disease in Taiwanese patients with Type 2 diabetes. *Diabet Med*. 2004;21:724-9.
- Bo S, Cavallo-Perin P, Gentile L, Repetti E, Pagano G. Hypouricemia and hyperuricemia in type 2 diabetes: two different phenotypes. *Eur J Clin Invest*. 2001;31:318-21.
- Wun YT, Chan CS, Lui CS. Hyperuricaemia in Type 2 diabetes mellitus. *Diabetes Nutr Metab*. 1999;12:286-91.
- Minami M, Ishiyama A, Takagi M, Omata M, Atarashi K. Effects of allopurinol, a xanthine oxidase inhibitor, on renal injury in hypercholesterolemia-induced hypertensive rats. *Blood Press*. 2005;14:120-5.
- Kang DH, Nakagawa T, Feng L, et al. A role for uric acid in the progression of renal disease. *J Am Soc Nephrol*. 2002;13:2888-97.
- Hostetter, TH. Prevention of end stage renal disease due to type 2 diabetes. *N Engl J Med* 2001; 345:410
- Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851-60.
- Atkins RC, Briganti EM, Lewis JB, et al. Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. *Am J Kidney Dis*. 2005;45:281-7.
- Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861-9.
- Barnett AH, Bain SC, Bouter P, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med*. 2004;351: 1952-61.
- Nielsen FS, Rossing P, Gall MA, Skott P, Smidt UM, Parving HH. Impact of lisinopril and atenolol on kidney function in hypertensive NIDDM subjects with diabetic nephropathy. *Diabetes*. 1994;43:1108-13.

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